

## **BUCCAL, POLAR AND NON-POLAR SPRAY CONTAINING TESTOSTERONE**

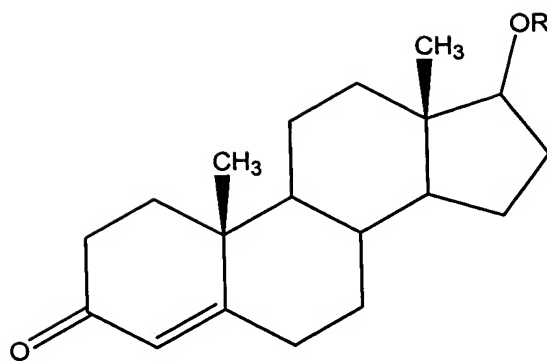
### **CROSS REFERENCE TO RELATED APPLICATIONS**

[0001] This application is a continuation-in-part of application no. 10/230,073, filed August 29, 2002, pending, which is a continuation-in-part of application no. 09/537,118, filed March 29, 2000, which is a continuation-in-part of the U.S. national phase designation of PCT/US97/17899, filed October 1, 1997, the disclosures of which are incorporated by reference herein in their entirety.

### **BACKGROUND OF THE INVENTION**

[0002] It is known that certain biologically active compounds are better absorbed through the oral mucosa than through other routes of administration, such as through the stomach or intestine. However, formulations suitable for such administration by these latter routes present their own problems. For example, the biologically active compound must be compatible with the other components of the composition such as propellants, solvents, etc. Many such formulations have been proposed. For example, U.S.P. 4,689,233, Dvorsky et al., describes a soft gelatin capsule for the administration of the anti-coronary drug nifedipine dissolved in a mixture of polyether alcohols. U.S.P. 4,755,389, Jones et al., describes a hard gelatin chewable capsule containing nifedipine. A chewable gelatin capsule containing a solution or dispersion of a drug is described in U.S.P. 4,935,243, Borkan et al. U.S.P. 4,919,919, Aouda et al, and U.S.P. 5,370,862, Klokke-Bethke, describe a nitroglycerin spray for administration to the oral mucosa comprising nitroglycerin, ethanol, and other components. An orally administered pump spray is described by Cholcha in U.S.P. 5,186,925. Aerosol compositions containing a hydrocarbon propellant and a drug for administration to a mucosal surface are described in U.K. 2,082,457, Su, U.S.P. 3,155,574, Silson et al., U.S.P. 5,011,678, Wang et al., and by Parnell in U.S.P. 5,128,132. It should be noted that these references discuss bioavailability of solutions by inhalation rather than through the membranes to which they are administered.

[0003] Testosterone is an androgen having the structure depicted below, wherein R is -H:



I

[0004] Testosterone is produced by the interstitial cells of the testes and is main androgen in the plasma of men. In women, testosterone is produced in low amounts in the ovary and adrenal gland. Androgen is metabolized to other hormonally active steroids, including dihydrotestosterone, in peripheral tissues so that the action of testosterone is actually the combined effect of testosterone itself and the metabolites of testosterone. (*Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 9<sup>th</sup> ed., pp. 1441).

[0005] Testosterone is used to treat hypogonadism in males (*Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 9<sup>th</sup> ed., pp. 1450-1451).

[0006] Administration of testosterone may also improve muscle development (*Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 9<sup>th</sup> ed., pp. 1451).

[0007] Administration of testosterone stimulates erythropoiesis to increase production of erythropoietin (*Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 9<sup>th</sup> ed., pp. 1452).

[0008] Testosterone has been used to treat anemias, especially those associated with failure of bone marrow, myelofibrosis, and renal failure (*Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 9<sup>th</sup> ed., pp. 1452).

[0009] Testosterone has been used to treat hereditary angioneurotic edema (*Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 9<sup>th</sup> ed., pp. 1452).

[0010] Testosterone has been used for the management of short stature resulting from growth retardation from causes other than pituitary deficiency (*Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 9<sup>th</sup> ed., pp. 1452-1453).

[0011] Testosterone has been used to treat carcinoma of the breast in women (*Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 9<sup>th</sup> ed., pp. 1453).

[0012] Testosterone has been used to treat osteoporosis (*Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 9<sup>th</sup> ed., pp. 1453).

[0013] Testosterone is difficult to administer by mouth or parenterally. Oral administration of testosterone is followed by absorption into the portal blood and degradation by the liver so that insufficient amounts of the hormone reach the systemic circulatory system. Parenteral administration also results in rapid metabolism. Accordingly, the testosterone molecule is often modified to retard the rate of catabolism or increase the androgenic potency of each molecule. For example, the testosterone molecule can be modified by esterifying the 17 $\beta$ -hydroxyl group or alkylating the 17 $\alpha$  position (*Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 9<sup>th</sup> ed., pp. 1442).

[0014] Other means of administering testosterone have also been used to avoid the problems associated with oral and parenteral administration such as transdermal patches, subcutaneous implantation, and biodegradable microcapsule formulations for injection (*Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 9<sup>th</sup> ed., pp. 1442).

[0015] Typically, a dosage should supply 6 to 10 mg of testosterone per day. This dose can be met, for example, by administering testosterone propionate (structure I, wherein R is -C(O)CH<sub>2</sub>CH<sub>3</sub>) by intramuscular injection as an oily solution at a dose of 25 mg three times per week (*Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 9<sup>th</sup> ed., pp. 1448).

#### SUMMARY OF THE INVENTION

[0016] A buccal aerosol spray or soft bite gelatin capsule using a polar or non-polar solvent has now been developed which provides biologically active compounds for rapid absorption through the oral mucosa, resulting in fast onset of effect.

[0017] The buccal aerosol spray compositions of the present invention, for transmucosal administration of a pharmacologically active compound soluble in a pharmacologically acceptable non-polar solvent comprise in weight % of total composition: pharmaceutically acceptable propellant 5-80 %, nonpolar solvent 19-85 %, active compound 0.05-50 %, suitably additionally comprising, by weight of total composition a flavoring agent 0.01-10 %. Preferably the composition comprises: propellant 10-70 %, non-polar solvent 25-89.9 %, active compound 0.01-40 %, flavoring agent 1-8 %; most suitably propellant 20-70 %, non-polar solvent 25-74.75 %, active compound 0.25-35 %, flavoring agent 2-7.5 %.

[0018] The buccal polar aerosol spray compositions of the present invention, for transmucosal administration of a pharmacologically active compound soluble in a pharmacologically acceptable polar solvent are also administrable in aerosol form driven by a propellant. In this case, the composition comprises in weight % of total composition: aqueous polar solvent 10-97 %, active compound 0.1-25 %, suitably additionally comprising, by weight of total composition a flavoring agent 0.05-10 % and propellant: 2 - 10 %. Preferably the composition comprises: polar solvent 20-97 %, active compound 0.1-15%, flavoring agent 0.1-5 % and propellant 2-5 %; most suitably polar solvent 25-97 %, active compound 0.2-25 %, flavoring agent 0.1-2.5 % and propellant 2-4 %.

[0019] In another embodiment, the buccal polar aerosol spray compositions of the present invention for transmucosal administration of a pharmacologically active compound (*i.e.*, those administrable in aerosol form driven by a propellant) comprises a mixture of a polar and a non-polar solvent comprising in weight % of total composition: solvent 10-97 %, active compound 0.05-50 %, propellant 5 -80 %, and optionally a taste mask and/or flavoring agent 0.01-10 %. Preferably the composition comprises: solvent 20-97 %, active compound 0.1-40 %, propellant 10-70 %, and taste mask and/or flavoring agent 1-8 %; most suitably solvent 25-97 %, active compound 0.25-35 %, propellant 20-70 %, and taste mask and/or flavoring agent 2-7.5 %. The ratio of the polar solvent to the non-polar solvent can range from about 1:99 to about 99:1, preferable from about 60:40 to about 40:60, and more preferably about 50:50.

[0020] The buccal pump spray composition of the present invention, *i.e.*, the propellant free composition, for transmucosal administration of a pharmacologically active compound wherein said active compound is soluble in a pharmacologically acceptable non-polar solvent comprises in weight % of total composition: non-polar solvent 30-99.69 %, active compound 0.005-55 %, and suitably additionally, flavoring agent 0.1-10 %.

[0021] The buccal polar pump spray compositions of the present invention, *i.e.*, the propellant free composition, for transmucosal administration of a pharmacologically active compound soluble in a pharmacologically acceptable polar solvent comprises in weight % of total composition: aqueous polar solvent 30-99.69 %, active compound 0.001-60 %, suitably additionally comprising, by weight of total composition a flavoring agent 0.1-10 %. Preferably the composition comprises: polar solvent 37-98.58 %, active compound 0.005-55 %, flavoring agent 0.5-8 %; most suitably polar solvent 60.9-97.06 %, active compound 0.01-40 %, flavoring agent 0.75-7.5 %.

**[0022]** In another embodiment, the buccal pump spray composition (*i.e.*, the propellant free composition) for transmucosal administration of a pharmacologically active compound comprises a mixture of a polar solvent and a non-polar solvent comprising in weight % of total composition solvent 30-99.69 %, active compound 0.001-60 %, and optionally a taste mask and/or flavoring agent 0.1-10 %. Preferably the composition comprises: solvent 37-98.58 %, active compound 0.005-55 %, taste mask and/or flavoring agent 0.5-8 %; more preferably the composition comprises solvent 60.9-97.06 %, active compound 0.01-40 %, and taste mask and/or flavoring agent 0.75-7.5 %. The ratio of the polar solvent to the non-polar solvent can range from about 1:99 to about 99:1, preferable about 60:40 to about 40:60, and more preferably about 50:50.

**[0023]** The soft bite gelatin capsules of the present invention for transmucosal administration of a pharmacologically active compound, at least partially soluble in a pharmacologically acceptable non-polar solvent, having charged thereto a fill composition comprise in weight % of total composition: non-polar solvent 4-99.99 %, emulsifier 0-20 %, active compound 0.01-80 %, provided that said fill composition contains less than 10 % of water, suitably additionally comprising, by weight of the composition: flavoring agent 0.01-10 %. Preferably, the soft bite gelatin capsule comprises: non-polar solvent 21.5-99.975 %, emulsifier 0-15 %, active compound 0.025-70 %, flavoring agent 1-8 %; most suitably: nonpolar solvent 28.5-97.9 %, emulsifier 0-10 %, active compound 0.1-65.0 %, flavoring agent 2-6 %.

**[0024]** The soft bite polar gelatin capsules of the present invention for transmucosal administration of a pharmacologically active compound, at least partially soluble in a pharmacologically acceptable polar solvent, having charged thereto a composition comprising in weight % of total composition: polar solvent 25-99.89 %, emulsifier 0-20 %, active compound 0.01-65 %, provided that said composition contains less than 10 % of water, suitably additionally comprising, by weight of the composition: flavoring agent 0.01-10 %. Preferably, the soft bite gelatin capsule comprises: polar solvent 37-99.95 %, emulsifier 0-15 %, active compound 0.025-55 %, flavoring agent 1-8 %; most suitably: polar solvent 44-96.925 %, emulsifier 0-10 %, active compound 0.075-50 %, flavoring agent 2-6 %.

**[0025]** It is an object of the invention to coat the mucosal membranes either with fine droplets of spray containing the active compounds or a solution or paste thereof from bite capsules.

[0026] It is also an object of the invention to administer to the oral mucosa of a mammalian in need of same, preferably man, by spray or bite capsule, a predetermined amount of a biologically active compound by this method or from a soft gelatin capsule.

[0027] A further object is a sealed aerosol spray container containing a composition of the non polar or polar aerosol spray formulation, and a metered valve suitable for releasing from said container a predetermined amount of said composition.

[0028] As the propellant evaporates after activation of the aerosol valve, a mist of fine droplets is formed which contains solvent and active compound.

[0029] The propellant is a non-Freon material, preferably a C<sub>3-8</sub> hydrocarbon of a linear or branched configuration. The propellant should be substantially non-aqueous. The propellant produces a pressure in the aerosol container such that under expected normal usage it will produce sufficient pressure to expel the solvent from the container when the valve is activated but not excessive pressure such as to damage the container or valve seals.

[0030] The non-polar solvent is a non-polar hydrocarbon, preferably a C<sub>7-18</sub> hydrocarbon of a linear or branched configuration, fatty acid esters, and triglycerides, such as miglyol. The solvent must dissolve the active compound and be miscible with the propellant, *i.e.*, solvent and propellant must form a single phase at a temperature of 0-40°C a pressure range of between 1-3 atm.

[0031] The polar and non-polar aerosol spray compositions of the invention are intended to be administered from a sealed, pressurized container. Unlike a pump spray, which allows the entry of air into the container after every activation, the aerosol container of the invention is sealed at the time of manufacture. The contents of the container are released by activation of a metered valve, which does not allow entry of atmospheric gases with each activation. Such containers are commercially available.

[0032] A further object is a pump spray container containing a composition of the pump spray formulation, and a metered valve suitable for releasing from said container a predetermined amount of said composition.

[0033] A further object is a soft gelatin bite capsule containing a composition of as set forth above. The formulation may be in the form of a viscous solution or paste containing the active compounds. Although solutions are preferred, paste fills may also be used where the active compound is not soluble or only partially soluble in the solvent of choice. Where water is used to form part of the paste composition, it should not exceed 10 % thereof. (All percentages herein are by weight unless otherwise indicated.)

[0034] The polar or non-polar solvent is chosen such that it is compatible with the gelatin shell and the active compound. The solvent preferably dissolves the active compound. However, other components wherein the active compound is not soluble or only slightly soluble may be used and will form a paste fill.

[0035] Soft gelatin capsules are well known in the art. See, for example, U.S.P. 4,935,243, Borkan et al., for its teaching of such capsules. The capsules of the present invention are intended to be bitten into to release the low viscosity solution or paste therein, which will then coat the buccal mucosa with the active compounds. Typical capsules, which are swallowed whole or bitten and then swallowed, deliver the active compounds to the stomach, which results in significant lag time before maximum blood levels can be achieved or subject the compound to a large first pass effect. Because of the enhanced absorption of the compounds through the oral mucosa and no chance of a first pass effect, use of the bite capsules of the invention will eliminate much of the lag time, resulting in hastened onset of biological effect. The shell of a soft gelatin capsule of the invention may comprise, for example: gelatin: 50-75 %, glycerin 20-30 %, colorants 0.5-1.5 %, water 5-10 %, and sorbitol 2-10 %.

[0036] The active compound may include, biologically active peptides, central nervous system active amines, sulfonyl ureas, antibiotics, antifungals, antivirals, sleep inducers, antiasthmatics, bronchial dilators, antiemetics, histamine H-2 receptor antagonists, barbiturates, prostaglandins and neutraceuticals.

[0037] The active compounds may also include antihistamines, alkaloids, hormones, benzodiazepines and narcotic analgesics. While not limited thereto, these active compounds are particularly suitable for non-polar pump spray formulation and application.

[0038] The active compounds may also include endocrine modulators, glucose production inhibitors, agents for treatment of type II diabetes, anti-secretory agents, glycolipids, glycoproteins, anti-hyperthyroid agents, thyroid hormones, or mixtures thereof.

[0039] In one embodiment, the active compound is testosterone or an ester thereof.

#### BRIEF DESCRIPTION OF THE DRAWING

[0040] FIG 1. is a schematic diagram showing routes of absorption and processing of pharmacologically active substances in a mammalian system.

#### DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0041] The preferred active compounds of the present invention are in an ionized, salt form or as the free base of the pharmaceutically acceptable salts thereof (provided, for

the aerosol or pump spray compositions, they are soluble in the spray solvent). These compounds are soluble in the non-polar solvents of the invention at useful concentrations or can be prepared as pastes at useful concentrations. These concentrations may be less than the standard accepted dose for these compounds since there is enhanced absorption of the compounds through the oral mucosa. This aspect of the invention is especially important when there is a large (40-99.99%) first pass effect.

[0042] As propellants for the non polar sprays, propane, N-butane, iso-butane, N-pentane, iso-pentane, and neo-pentane, and mixtures thereof may be used. N-butane and iso-butane, as single gases, are the preferred propellants. It is permissible for the propellant to have a water content of no more than 0.2%, typically 0.1-0.2%. All percentages herein are by weight unless otherwise indicated. It is also preferable that the propellant be synthetically produced to minimize the presence of contaminants which are harmful to the active compounds. These contaminants include oxidizing agents, reducing agents, Lewis acids or bases, and water. The concentration of each of these should be less than 0.1 %, except that water may be as high as 0.2%.

[0043] Suitable non-polar solvents for the capsules and the non-polar sprays include (C<sub>2</sub>-C<sub>24</sub>) fatty acid (C<sub>2</sub>-C<sub>6</sub>) esters, C<sub>7</sub>-C<sub>18</sub> hydrocarbon, C<sub>2</sub>-C<sub>6</sub> alkanoyl esters, and the triglycerides of the corresponding acids. When the capsule fill is a paste, other liquid components may be used instead of the above low molecular weight solvents. These include soya oil, corn oil, other vegetable oils.

[0044] As solvents for the polar capsules or sprays there may be used low molecular weight polyethyleneglycols (PEG) of 400-1000 Mw (preferably 400-600), low molecular weight (C<sub>2</sub>-C<sub>8</sub>) mono and polyols and alcohols of C<sub>7</sub>-C<sub>18</sub> linear or branch chain hydrocarbons, glycerin may also be present and water may also be used in the sprays, but only in limited amount in the capsules.

[0045] It is expected that some glycerin and water used to make the gelatin shell will migrate from the shell to the fill during the curing of the shell. Likewise, there may be some migration of components from the fill to the shell during curing and even throughout the shelf-life of the capsule.

[0046] Therefore, the values given herein are for the compositions as prepared, it being within the scope of the invention that minor variations will occur.



**[0047]** The preferred flavoring agents are synthetic or natural oil of peppermint, oil of spearmint, citrus oil, fruit flavors, sweeteners (sugars, aspartame, saccharin, etc.), and combinations thereof.

**[0048]** The compositions may further include a taste mask. The term “taste mask” as used herein means an agent that can hide or minimize an undesirable flavor such as a bitter or sour flavor. A representative taste masks is a combination of vanillin, ethyl vanillin, maltol, iso-amyl acetate, ethyl oxyhydrate, anisic aldehyde, and propylene glycol (commercially available as “PFC 9885 Bitter Mask” from Pharmaceutical Flavor Clinic of Camden, NJ). A taste mask in combination with a flavoring agent is particularly advantageous when the active compound is an alkaloid since alkaloids often have a bitter taste.

**[0049]** The active substances include the active compounds selected from the group consisting of cyclosporine, sermorelin, octreotide acetate, calcitonin-salmon, insulin lispro, sumatriptan succinate, clozapine, cyclobenzaprine, dexfenfluramine hydrochloride, glyburide, zidovudine, erythromycin, ciprofloxacin, ondansetron hydrochloride, dimenhydrinate, cimetidine hydrochloride, famotidine, phenytoin sodium, phenytoin, carboprost thromethamine, carboprost, diphenhydramine hydrochloride, isoproterenol hydrochloride, terbutaline sulfate, terbutaline, theophylline, albuterol sulfate and neutraceuticals, that is to say nutrients with pharmacological action such as but not limited

**[0050]** In another embodiment, the active compound is an endocrine modulator, glucose production inhibitor, agent for treatment of type II diabetes, anti-secretory agent, glycolipid, glycoprotein, anti-hyperthyroid agent, thyroid hormone, or a mixture thereof.

**[0051]** In one embodiment the active compound is an endocrine modulator. Suitable endocrine modulators for use in the buccal sprays of the invention include, but are not limited to, methimazole, voglibose, finasteride, GI198745, liothyronine, glyburide, metformin, nateglinide, ioglitazone, pegvisomant, minoxidil, and mixtures thereof.

**[0052]** In one embodiment the active compound is a glucose production inhibitor. Suitable glucose production inhibitors for use in the buccal sprays of the invention include, but are not limited to, acarbose, acetohexamide, chlorpropamide, glipizide, glyburide, metformin, miglitol, nateglinide, pioglitazone, rosiglitazone, tolbutamide, tolazamide, and mixtures thereof.

**[0053]** In one embodiment the active compound is an agent for treatment of type II diabetes. Suitable agents for treatment of type II diabetes for use in the buccal sprays of the

invention include, but are not limited to, acarbose, acetohexamide, chlorpropamide, glipizide, glyburide, metformin, miglitol, nateglinide, pioglitazone, rosiglitazone, tolbutamide, tolazamide, and mixtures thereof.

**[0054]** In one embodiment the active compound is an anti-secretory agent. Suitable anti-secretory agents for use in the buccal sprays of the invention include, but are not limited to, esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole, tenetoprazole, ecabet, misoprostol, teprenone, and mixtures thereof.

**[0055]** In one embodiment the active compound is a glycolipid. Suitable glycolipids for use in the buccal sprays of the invention include, but are not limited to imigulcerase, vancomycin, vevesca (OGT 918), GMK vaccine, and mixtures thereof.

**[0056]** In one embodiment the active compound is a glycoprotein. Suitable glycoproteins for use in the buccal sprays of the invention include, but are not limited to, staphvax, bimosiamose (TBC1269), GCS-100, heparin, and mixtures thereof.

**[0057]** In one embodiment the active compound is an anti-hyperthyroid agent. Suitable anti-hyperthyroid agents for use in the buccal sprays of the invention include, but are not limited to, methimazol, propylthiouracil, and mixtures thereof.

**[0058]** In one embodiment the active compound is a thyroid hormone. A suitable thyroid hormone for use in the buccal sprays of the invention includes, but is not limited to, levothyroxine.

**[0059]** In one embodiment, the active compound is testosterone or a pharmaceutically acceptable ester thereof. Typically, when the active compound is testosterone or a pharmaceutically acceptable ester thereof the buccal spray composition contains from about 0.01 to 20 weight/weight (w/w) percent testosterone, preferably, about 0.1 to 15 w/w percent, and more preferably about 0.2 to 10 w/w percent testosterone or a pharmaceutically acceptable ester thereof.

**[0060]** Suitable esters of testosterone that can be used in the compositions and methods of the invention. These include, but are not limited to, testosterone propionate (Testex®), testosterone enanthate (Delatestry®), and testosterone cypionate (Depo-testosterone®).

**[0061]** The invention further relates to a method of treating hypogonadism in a patient by spraying the oral mucosa of the patient with a therapeutically effective amount of a buccal spray comprising testosterone or a pharmaceutically acceptable ester thereof.

**[0062]** The invention further relates to a method of improving muscle development in a patient by spraying the oral mucosa of the patient with a therapeutically effective amount of a buccal spray comprising testosterone or a pharmaceutically acceptable ester thereof.

**[0063]** The invention further relates to a method of stimulating erythropoiesis in a patient by spraying the oral mucosa of the patient with a therapeutically effective amount of a buccal spray comprising testosterone or a pharmaceutically acceptable ester thereof.

**[0064]** The invention further relates to a method of treating anemia in a patient by spraying the oral mucosa of the patient with a therapeutically effective amount of a buccal spray comprising testosterone or a pharmaceutically acceptable ester thereof. In one embodiment, the anemia is associated with failure of bone marrow, myelofibrosis, or renal failure.

**[0065]** The invention further relates to a method of treating angioneurotic edema in a patient by spraying the oral mucosa of the patient with a therapeutically effective amount of a buccal spray comprising testosterone or a pharmaceutically acceptable ester thereof.

**[0066]** The invention further relates to a method of treating growth retardation in a patient by spraying the oral mucosa of the patient with a therapeutically effective amount of a buccal spray comprising testosterone or a pharmaceutically acceptable ester thereof.

**[0067]** The invention further relates to a method of treating carcinoma of the breast in a women by spraying the oral mucosa of the women with a therapeutically effective amount of a buccal spray comprising testosterone or a pharmaceutically acceptable ester thereof.

**[0068]** The invention further relates to a method of treating osteoporosis in a patient by spraying the oral mucosa of the patient with a therapeutically effective amount of a buccal spray comprising testosterone or a pharmaceutically acceptable ester thereof.

**[0069]** The formulations of the present invention comprise an active compound or a pharmaceutically acceptable salt thereof. The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic acids or bases including organic and inorganic acids or bases.

**[0070]** When an active compound of the present invention is acidic, salts may be prepared from pharmaceutically acceptable non-toxic bases. Salts derived from all stable forms of inorganic bases include aluminum, ammonium, calcium, copper, iron, lithium, magnesium, manganese, potassium, sodium, zinc, etc. Particularly preferred are the

ammonium, calcium, magnesium, potassium, and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion-exchange resins such as arginine, betaine, caffeine, choline, N,N dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethyl-aminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, isopropylamine, lysine, methyl-glucosamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purine, theobromine, triethylamine, trimethylamine, tripropylamine, etc.

[0071] When an active compound of the present invention is basic, salts may be prepared from pharmaceutically acceptable non-toxic acids. Such acids include acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethane-sulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic, etc. Particularly preferred are citric, hydrobromic, maleic, phosphoric, sulfuric, and tartaric acids.

[0072] In the discussion of methods of treatment herein, reference to the active compounds is meant to also include the pharmaceutically acceptable salts thereof. While certain formulations are set forth herein, the actual amounts to be administered to the mammal or man in need of same are to be determined by the treating physician.

[0073] The invention is further defined by reference to the following examples, which are intended to be illustrative and not limiting.

[0074] The following are examples of certain classes. All values unless otherwise specified are in weight percent.

## EXAMPLES

### EXAMPLE 1

#### Biologically active peptides including peptide hormones

##### A. Cyclosporine lingual spray

	Amounts	preferred amount	most preferred amount
cyclosporine	5-50	10-35	15-25
water	5-20	7.5-50	9.5-12
ethanol	5-60	7.5-50	10-20
polyethylene glycol	20-60	30-45	35-40
flavors	0.1-5	1-4	2-3

##### B. Cyclosporine Non-Polar lingual spray

	Amounts	preferred amount	most preferred amount
cyclosporine	1-50	3-40	5-30
Migylol	20	25	30-40
Polyoxyethylated castor oil	20	25	30-40
Butane	25-80	30-70	33-50
flavors	0.1-5	1-4	2-3

##### C. Cyclosporine non-polar bite caosule

	Amounts	preferred amount	most preferred amount
cyclosporine	1-35	5-25	10-20
olive oil	25-60	35-55	30-45
polyoxyethylated oleic glycerides	25-60	35-55	30-45
flavors	0.1-5	1-4	2-3

D. Cyclosporine bite capsule

	Amounts	preferred amount	most preferred amount
cyclosporine	5-50	10-35	15-25
polyethylene glycol	20-60	30-45	35-40
glycerin	5-30	7.5-25	10-20
propylene glycol	5-30	7.5-25	10-20
flavors	0.1-10	1-8	3-6

E. Sermorelin (as the acetate) lingual spray

	Amounts	preferred amount	most preferred
sermorelin (as the acetate)	.01-5	.1-3	.2-1.0
mannitol	1-25	5-20	10-15
monobasic sodium phosphate,	0.1-5	1-3 1	.5-2.5
dibasic sodium phosphate water	0.01-5	.05-3	0.1-0.5
ethanol	5-30	7.5-25	9.5-15
polyethylene glycol	20-60	30-45	35-40
propylene glycol	5-25	10-20	12-17
flavors	0.1-5	1-4	2-3

F. Octreotide acetate (Sandostatin) lingual spray

	Amounts	preferred amount	most preferred amount
octreotide acetate	0.001-0.5	0.005-0.250	0.01-0.10
acetic acid	1-10	2-8	4-6
sodium acetate	1-10	2-8	4-6
sodium chloride	3-30	.5-25	15-20
flavors	0.1-5	0.5-.4	2-3
ethanol	5-30	7.5-20	9.5-15
water	15-95	35-90	65-85
flavors	0.1-5	1-4	2-3

G. Calcitonin-salmon lingual spray

	Amounts	preferred amount	most preferred amount
calcitonin-salmon	0.001-5	0.005-2	01-1.5
ethanol	2-15	3-10	7-9.5
water	30-95	50-90	60-80
polyethylene glycol	2-15	3-10	7-9.5
sodium chloride	2.5-20	5-15	10-12.5
flavors	0.1-5	1-4	2-3

H. Insulin lispro, lingual spray

	Amounts	preferred amount	most preferred amount
insulin	20-60	4-55	5-50
glycerin	0.1-10	0.25-5	0.1-1.5
dibasic sodium phosphate	1-15	2.5-10	4-8
m-cresol,	1-25	5-25	7.5-12.5
zinc oxide	0.01-0.25	.05-0.15	0.075-0.10
m-cresol	0.1-1	0.2-0.8	0.4-0.6
phenol	trace amounts	trace amounts	trace amounts
ethanol	5-20	7.5-15	9-12
water	30-90	40-80	50-75
propylene glycol	5-20	7.5-15	9-12
flavors	0.1-5	0.5-3	0.75-2
adjust pH to 7.0-7.8 with HCl or NaOH			



## EXAMPLE 2

CNS active amines and their salts: including but not limited to tricyclic amines, GABA analogues, thiazides, phenothiazine derivatives, serotonin antagonists and serotonin reuptake inhibitors

### A. Sumatriptan succinate lingual spray

	Amounts	preferred amount	most preferred amount
sumatriptan succinate	0.5-30	1-20	10-15
ethanol	5-60	7.5-50	10-20
propylene glycol	5-30	7.5-20	10-15
polyethylene glycol	0-60	30-45	35-40
water	5-30	7.5-20	10-15
flavors	0.1-5	1-4	2-3

### B. Sumatriptan succinate bite capsule

	Amounts	preferred amount	most preferred amount
sumatriptan succinate	0.01-5	0.05-3.5	0.075-1.75
polyethylene glycol	25-70	30-60	35-50
glycerin	25-70	30-60	35-50
flavors	0.1-10	1-8	3-6

C. Clozepine lingual spray

	Amounts	preferred amount	most preferred amount
clozepine	0.5-30	1-20	10-15
ethanol	5-60	7.5-50	10-20
propylene glycol	5-30	7.5-20	10-15
polyethylene glycol	0-60	30-45	35-40
water	5-30	7.5-20	10-15
flavors	0.1-5	1-4	2-3

D. Clozepine non-polar lingual spray with propellant

	Amounts	preferred amount	most preferred amount
clozepine	0.5-30	1-20	10-15
Migylol	20-85	25-70	30-40
Butanol	5-80	30-75	60-70
flavors	0.1-5	1-4	2-3

E. Clozepine non-polar lingual spray without propellant

	Amounts	preferred amount	most preferred amount
clozepine	0.5-30	1-20	10-15
Migylol	70-99.5	80-99	85-90
flavors	0.1-5	1-4	2-3

F. Cyclobenzaprine non-polar lingual spray

	Amounts	preferred amount	most preferred amount
cyclobenzaprine (base)	0.5-30	1-20	10-15
Migylol	20-85	25-70	30-40
Iso-butane	15-80	30-75	60-70
Flavors	0.1-5	1-4	2-3

G. Dexfenfluramine hydrochloride lingual spray

	Amounts	preferred amount	most preferred amount
dexfenfluramine HCl	5-30	7.5-20	10-15
ethanol	5-60	7.5-50	10-20
propylene glycol	5-30	7.5-20	10-15
polyethylene glycol	0-60	30-45	35-40
water	5-30	7.5-20	10-15
flavors	0.1-5	1-4	2-3

### EXAMPLE 3

#### Sulfonylureas

##### A. Glyburide lingual spray

	Amounts	preferred amount	most preferred amount
glyburide	0.25-25	0.5-20	0.75-15
ethanol	5-60	-7.5-50	10-20
propylene glycol	5-30	7.5-20	10-15
polyethylene glycol	0-60	30-45	35-40
water	2.5-30	5-20	6-15
flavors	0.1-5	1-4	2-3

##### B. Glyburide non-polar bite capsule

	Amounts	preferred amount	most preferred amount
glyburide	0.01-10	0.025-7.5	0.1-4
olive oil	30-60	35-55	30-50
polyoxyethylated oleic glycerides	30-60	35-55	30-50
flavors	0.1-5	1-4	2-3

## EXAMPLE 4

### Antibiotics anti-fungals and anti-virals

A. Zidovudine [formerly called azidothymidine (AZT) (Retrovir)] non-polar lingual spray

	Amounts	preferred amount	most preferred amount
zidovudine	10-50	15-40	25-35
Soya oil	20-85	25-70	30-40
Butane	15-80	30-75	60-70
flavors	0.1-5	1-4	2-3

B. Erythromycin bite capsule bite capsule

	Amounts	preferred amount	most preferred amount
erythromycin	25-65	30-50	35-45
polyoxyethylene glycol	5-70	30-60	45-55
glycerin	5-20	7.5-15	10-12.5
flavors	1-10	2-8	3-6

C. Ciprofloxacin hydrochloride bite capsule

	Amounts	preferred amount	most preferred amount
ciprofloxacin hydrochloride	25-65	35-55	40-50
glycerin	5-20	7.5-15	10-12.5
polyethylene glycol	120-75	30-65	40-60
flavors	1-10	2-8	3-6

D. zidovudine [formerly called azidothymidine (AZT) (Retrovir)] lingual spray

	Amounts	preferred amount	most preferred amount
zidovudine	10-50	15-40	25-35
water	30-80	40-75	45-70
ethanol	5-20	7.5-15	9.5-12.5
polyethylene glycol	5-20	7.5-15	9.5-12.5
flavors	0.1-5	1-4	2-3

## EXAMPLE 5

### Anti-emetics

#### A. Ondansetron hydrochloride lingual spray

	Amounts	preferred amount	most preferred amount
ondansetron hydrochloride	1-25	2-20	2.5-15
citric acid monohydrate	1-10	2-8	2.5-5
sodium citrate dihydrate	0.5-5	1-4	1.25-2.5
water	1-90	5-85	10-75
ethanol	5-30	7.5-20	9.5-15
propylene glycol	5-30	7.5-20	9.5-15
polyethylene glycol	5-30	7.5-20	9.5-15
flavors	1-10	3-8	5-7.5

#### B. Dimenhydrinate bite capsule

	Amounts	preferred amount	most preferred amount
dimenhydrinate	0.5-30	2-25	3-15
glycerin	5-20	7.5-15	10-12.5
polyethylene glycol	45-95	50-90	55-85
flavors	1-10	2-8	3-6

#### C. Dimenhydrinate polar lingual spray

	Amounts	preferred amount	most preferred amount
dimenhydrinate	3-50	4-40	5-35
water	5-90	10-80	15-75
ethanol	1-80	3-50	5-10
polyethylene glycol	1-80	3-50	5-15
sorbitol	0.1-5	0.2-40	0.4-1.0
aspartame	0.01-0.5	0.02-0.4	0.04-0.1
flavors	0.1-5	1-4	2-3

## EXAMPLE 6

### Histamine H-2 receptor antagonists

#### A. Cimetidine hydrochloride bite capsule

	Amounts	preferred amount	most preferred amount
cimetidine HCl	10-60	15-55	25-50
glycerin	5-20	7.5-15	10-12.5
polyethylene glycol	20-90	25-85	30-75
flavors	1-10	2-8	3-6

#### B. Famotidine lingual spray

	Amounts	preferred amount	most preferred amount
famotidine	1-35	5-30	7-20
water	2.5-25	3-20	5-10
L-aspartic acid	0.1-20	1-15	5-10
polyethylene glycol	20-97	30-95	50-85
flavors	0.1-10	1-7.5	2-5

#### C. Famotidine non-polar lingual spray

	Amounts	preferred amount	most preferred amount
famotidine	1-35	5-30	7-20
Soya oil	10-50	15-40	15-20
Butane1	5-80	30-75	45-70
polyoxyethylated oleic glycerides	10-50	15-40	15-20
flavors	0.1-5	1-4	2-3



## EXAMPLE 7

### Barbiturates

#### A. Phenytoin sodium lingual spray

	Amounts	preferred amount	most preferred amount
phenytoin sodium	10-60	15-55	20-40
water	2.5-25	3-20	5-10
ethanol	5-30	7.5-20	9.5-15
propylene glycol	5-30	7.5-20	9.5-15
polyethylene glycol	5-30	7.5-20	9.5-15
flavors	1-10	3-8	5-7.5

#### B. Phenytoin non-polar lingual spray

	Amount	preferred amount	most preferred amount
phenytoin	5-45	10-40	15-35
migylol	10-50	15-40	15-20
Butane	15-80	30-75	60-70
polyoxyethylated oleic glycerides	10-50	15-40	15-20
flavors	0.1-10	1-8	5-7.5

## EXAMPLE 8

### Prostaglandins

#### A. Carboprost thromethamine lingual spray

	Amounts	preferred amount	most preferred amount
carboprost thromethamine	0.05-5	0.1-3	0.25-2.5
water	50-95	60-80	65-75
ethanol	5-20	7.5-15	9.5-12.5
polyethylene glycol	5-20	7.5-15	9.5-12.5
sodium chloride	1-20	3-15	4-8
flavors	0.1-5	1-4	2-3

pH is adjusted with sodium hydroxide and/or hydrochloric acid

#### B. Carboprost non-polar lingual spray

	Amounts	preferred amount	most preferred amount
carboprost	0.05-5	0.1-3	0.25-2.5
migylol	25-50	30-45	35-40
Butane	5-60	10-50	20-35
polyoxyethylated	25-50	30-45	35-40
oleic glycerides			
flavors	0.1-10	1-8	5-7.5

## EXAMPLE 9

### Neutraceuticals

#### A. Carnitine as bite capsule (contents are a paste)

	Amounts	preferred amount	most preferred amount
carnitine fumarate	6-80	30-70	45-65
soya oil	7.5-50	10-40	12.5-35
soya lecithin	0.001-1.0	0.005-0.5	.01-0.1
Soya fats	7.5-50	10-40	12.5-35
flavors	1-10	2-8	3-6

#### B. Valerian as lingual spray

	Amounts	preferred amount	most preferred amount
valerian extract	0.1-10	0.2-7	0.25-5
water	50-95	60-80	65-75
ethanol	5-20	7.5-15	9.5-12.5
polyethylene glycol	5-20	7.5-15	9.5-12.5
flavors	1-10	2-8	3-6

#### C. Echinacea as bite capsule

	Amounts	preferred amount	most preferred amount
echinacea extract	30-85	40-75	45-55
soya oil	7.5-50	10-40	12.5-35
soya lecithin	0.001-1.0	0.005-0.5	.01-0.1
Soya fats	7.5-50	10-40	12.5-35
flavors	1-10	2-8	3-6

D. Mixtures of ingredients

	Amounts	preferred amount	most preferred amount
magnesium oxide	15-40	20-35	25-30
chromium picolinate	0.01-1.0	0.02-0.5	.025-0.75
folic acid	.025-3.0	0.05-2.0	0.25-0.5
vitamin B-12	0.01-1.0	0.02-0.5	.025-0.75
vitamin E	15-40	20-35	25-30
Soya oil	10-40	12.5-35	15-20
soya lecithin	0.1-5	0.2-4	0.5-1.5
soya fat	10-40	15-35	17.5-20

## EXAMPLE 10

### Sleep Inducers (also CNS active amine)

#### A. Diphenhydramine hydrochloride lingual spray

	Amounts	preferred amount	most preferred amount
diphenhydramine	3-50.	4-40	5-35
HCl water	5-90	10-80	50-75
ethanol	1-80	3-50	5-10
polyethylene glycol	1-80	3-50	5-15
Sorbitol	0.1-5	0.2-4	0.4-1.0
aspartame	0.01-0.5	0.02-0.4	0.04-0.1
flavors	0.1-5	1-4	2-3

## EXAMPLE 11

### Anti-Asthmatics-Bronchodilators

#### A. Isoproterenol Hydrochloride as polar lingual spray

	Amounts	preferred amount	most preferred amount
isoproterenol Hydrochloride	0.1-10	0.2-7.5	0.5-6
water	5-90	10-80	50-75
ethanol	1-80	3-50	5-10
polyethylene glycol	1-80	3-50	5-15
Sorbitol	0.1-5	0.2-4	0.4-1.0
aspartame	0.01-0.5	0.02-0.4	0.04-0.1
flavors	0.1-5	1-4	2-3

#### B. Terbutaline sulfate as polar lingual spray

	Amounts	preferred amount	most preferred amount
terbutaline sulfate	0.1-10	0.2-7.5	0.5-6
water	5-90	10-80	50-75
ethanol	1-10	2-8	2.5-5
Sorbitol	0.1-5	0.2-4	0.4-1.0
aspartame	0.01-0.5	0.02-0.4	0.04-0.1
flavors	0.1-5	1-4	2-3

C. Terbutaline as non-polar lingual spray

	Amounts	preferred amount	most preferred amount
terbutaline	0.1-10	0.2-7.5	0.5-6
migylol	25-50	30-45	35-40
isobutane	5-60	10-50	20-35
polyoxyethylated oleic glycerides	25-50	30-45	35-40
flavors	0.1-10	1-8	5-7.5

D. Theophylline polar bite capsule

	Amounts	preferred amount	most preferred amount
theophylline	5-50	10-40	15-30
polyethylene glycol	20-60	25-50	30-40
glycerin	25-50	35-45	30-40
propylene glycol	25-50	35-45	30-40
flavors	0.1-5	1-4	2-3

E. Albuterol sulfate as polar lingual spray

	Amounts	preferred amount	most preferred amount
albuterol sulfate	0.1-10	0.2-7.5	0.5-6
water	5-90	10-80	50-75
ethanol	1-10	2-8	2.5-5
Sorbitol	0.1-5	0.2-4	0.4-1.0
aspartame	0.01-0.5	0.02-0.4	0.04-0.1
flavors	0.1-5	1-4	2-3

### Example 12

Polar solvent formulations using a propellant:

A. Sulfonylurea

	Amount	Preferred Amount	Most-Preferred Amount
glyburide	0.1-25%	0.5-15%	0.6-10%
Ethanol	40-99%	60-97%	70-97%
Water	0.01-5%	0.1-4%	0.2-2%
Flavors	0.05-10%	0.1-5%	0.1-2.5%
Propellant	2-10%	3-5%	3-4%

B. Prostaglandin E (vasodilator)

	Amount	Preferred Amount	Most-Preferred Amount
prostaglandin E <sub>1</sub>	0.01-10%	0.1-5%	0.2-3%
Ethanol	10-90%	20-75%	25-50%
Propylene glycol	1-90%	5-80%	10-75%
Water	0.01-5%	0.1-4%	0.2-2%
Flavors	0.05-10%	0.1-5%	0.1-2.5%
Propellant	2-10%	3-5%	3-4%

C. Promethazine (antiemetic, sleep inducer, and CNS active amine)

	Amount	Preferred Amount	Most-Preferred Amount
promethazine	1-25%	3-15%	5-12%
Ethanol	10-90%	20-75%	25-50%
Propylene glycol	1-90%	5-80%	10-75%
Water	0.01-5%	0.1-4%	0.2-2%
Flavors	0.05-10%	0.1-5%	0.1-2.5%
Propellant	2-10%	3-5%	3-4%



D.     Meclizine

	Amount	Preferred Amount	Most-Preferred Amount
meclizine	1-25%	3-15%	5-12%
Ethanol	1-15%	2-10%	3-6
Propylene glycol	20-98%	5-90%	10-85%
Water	0.01-5%	0.1-4%	0.2-2%
Flavors	0.05-10%	0.1-5%	0.1-2.5%
Propellant	2-10%	3-5%	3-4%

Example 13  
Testosterone Formulations

A. A propellant free testosterone formulation in a polar solvent has the following formula:

Ingredient	Percent (w/w)
Testosterone	4
Oleic Acid	1
Polyethylene glycol 200	50
Ethanol	45

B. A propellant free testosterone formulation in a mixture of a polar solvent and a non-polar solvent has the following formula:

Ingredient	Percent (w/w)
Testosterone	4
Miglyol 810	40
Oleic acid	1
Benzalkonium chloride	1
Lemon oil	1
A-tocopherol acetate	1
Ethanol	52

C. A testosterone formulation in a polar solvent with a propellant can be made according to the following formula.

Ingredient	Percent (w/w)
Testosterone	4
Oleic acid	1
Flavor	1
Ethanol	30
Butane	Qs to 100

D. A propellant free testosterone formulation in a non-polar solvent can be made according to the following formula:

Ingredient	Percent (w/w)
Testosterone	4
Flavor	1
Oleic acid	1
Miglyol	Qs to 100

E. A testosterone formulation in non-polar solvent with a propellant can be made according to the following formula:

Ingredient	Percent (w/w)
Testosterone	4
Miglyol 810	4
Oleic acid	40
Lemon oil	1
Butane	Qs 1to 100

F. A testosterone formulation in a mixture of a polar solvent and a non-polar solvent with a propellant can be made according to the following formula:

Ingredient	Percent (w/w)
Testosterone	4
Miglyol 810	20
Oleic acid	1
Bitter mask	1
Ethanol	20
Butane	Qs 1to 100